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Comparison of clinical outcomes of intensive care patients with COVID-19 pneumonia receiving and not receiving tocilizumab treatment

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ABSTRACT

Aim: In patients with Coronavirus disease 2019 (COVID-19) infection, a situation called cytokine storm and an increase in proinflammatory cytokines such as interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-1 (IL-1) in the blood has been observed and it has been found that this is clinically related to the development of severe disease. Therefore, tocilizumab (TCZ) therapy that blocks IL-6 will reduce the immunological response and thus potentially harm caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The aim of this study is to determine the effect of TCZ treatment on length of hospital stay, need for invasive mechanical ventilation and mortality in COVID-19 patients followed in the tertiary intensive care unit.

Material and Method: This retrospective cross-sectional study was conducted among patients hospitalized with the diagnosis of COVID-19 pneumonia between 01.09.2020 and 01.01.21 in intensive care units. Data were analyzed and evaluated separately in patients who received and did not receive TCZ treatment. Patients older than 18 years of age, who were hospitalized for at least 24 hours with the diagnosis of COVID-19 pneumonia and needed ≥36 hours of oxygen therapy, were not referred to another health center, were included in this study. Pregnant and lactating women were not included in the study. Patients with missing at least one data in the parameters to be evaluated were excluded from the study. Patients treated with an IL-6 inhibitor other than TCZ were excluded.

Results: After excluding patients who did not meet the inclusion criteria, 565 patients were included in the study. It was found that patients who received TCZ treatment after propensity score matching (PSM) had a significantly higher mean age (P<0.001) and lower obesity rates (P=0.002). There was no significant difference between the patients who received and did not receive TCZ treatment in terms of mechanical ventilation need, length of hospital stay and mortality (P=0.505, P=0.661, P=0.834).

Conclusion: As a result of our research, it was seen that TCZ treatment did not affect the need for invasive mechanical ventilation, hospital and intensive care unit stay, and mortality.

Keywords: COVID-19, pneumonia, tocilizumab, intensive care unit

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with high morbidity and mortality and impairing quality of life (1,2). The first case of pneumonia due to COVID-19 emerged in December 2019 in Wuhan city of China's Hubei province (3). The World Health Organization (WHO) declared a pandemic on March 11, 2020, after the disease spread rapidly around the world and cases emerged on all continents (4).

In COVID-19 infection, the emergence of an uncontrolled and excessive host immune response called cytokine storm syndrome is thought to be associated with the development of severe disease (5). It has been shown that the levels of proinflammatory cytokines such as interleukin-1 (IL-1), interleukin-8 (IL-8), especially interleukin-6 (IL-6), increase in the circulation in cytokine storm syndrome (6).

Treatments for COVID-19 infection, for which there is no definitive cure yet, are usually in the form of

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supportive treatments. Anti-cytokine treatments targeting suppression of proinflammatory cytokines have been started to be applied in order to control cytokine storm syndrome, especially in people with severe or critical illness. For this purpose, IL-6 inhibitors, IL-1 inhibitors and kinase inhibitors, which are frequently used in COVID-19 patients, especially in autoimmune and autoinflammatory diseases, are applied (7).

IL-6 is a proinflammatory cytokine that plays a major role in the pathogenesis of COVID-19 associated cytokine storm syndrome. IL-6 is produced by nearly all stromal cells and immune system cells (T lymphocytes, B lymphocytes, macrophage, dendritic cell, monocytes, mast cells) (8). IL-6 plays a role in B cell differentiation, acute phase response, increase and activation of T cell population, and angiogenesis (9). While circulating IL-6 levels in healthy individuals are extremely low (in the range of 1–5 pg/mL), IL-6 levels have been found to be increased in many inflammatory conditions associated with cytokine release (10).

Tocilizumab (TCZ), sarilumab, siltuximab are IL-6 antagonists with different pharmacological properties. TCZ is an IgG1 type recombinant humanized monoclonal antibody against the IL-6 receptor, which binds to both membrane-bound and soluble IL-6 receptors and inhibits signal transduction mediated by these receptors (8). TCZ is approved for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis (11). It has been shown that IL-6 production increases with the stimulation of immune cells by SARS-CoV-2, and especially high plasma IL-6 levels in COVID-19 patients with severe disease presentation (8). Establishing the relationship between the course of proinflammatory responses, associated disease symptoms and clinical pictures is an important algorithm in treatment approaches. Therefore, TCZ therapy that blocks IL-6 will reduce the immunological response and thus potentially harm caused by SARS-CoV-2.

The underlying hypothesis of our study was that IL-6 receptor blocking TCZ treatment would prevent serious disease outcomes by disrupting the cytokine storm associated with COVID-19 in patients hospitalized in the intensive care unit for COVID-19 pneumonia who do not need invasive mechanical ventilation yet. The aim of this study is to evaluate and compare the length of stay in the intensive care unit, length of stay in inpatient services, need for invasive mechanical ventilator support, complications and mortality rates of patients who received and did not receive TCZ treatment for COVID-19 pneumonia in intensive care units.

MATERIAL AND METHOD

Ethical Approval

This retrospective cross-sectional study was carried out in Uşak University Medical Faculty Clinical Researches Ethics Committee (Date: 15.06.2022, Decision No: 108-108-06). This study was conducted in accordance with the Declaration of Helsinki. Written informed consent was waived due to the retrospective nature of the study.

Study Design and Population

A retrospective observational analysis of electronic medical records of COVID-19 patients admitted to a public tertiary hospital was performed. This study was conducted among patients hospitalized with the diagnosis of COVID-19 pneumonia between 01.09.2020 and 01.01.21 in intensive care units.

Consecutive adults aged 18 and over years admitted with X ray confirmed pneumonia caused by laboratory confirmed COVID-19 infection were suitable for the study. Data concerning demographic, medical study, laboratory findings and treatment during hospital stay, admissions and outcomes were extracted from electronic medical records. Patients with TCZ were identified from pharmacy records of all patients to whom TCZ was dispensed. The observation period ended at final discharge.

In this study, patients younger than 18 years of age, pregnant and lactating women, patients referred to another health center, and patients with at least one missing data on the parameters to be evaluated were excluded from the study. Patients hospitalized for <24 h or those with no need of oxygen therapy for >36 h were excluded. Patients treated with an IL-6 inhibitor other than TCZ were excluded from the study. All patients included in the study meet the TCZ treatment criteria for the treatment of COVID-19 infection in accordance with the Turkish Ministry of Health guidance during the study period (12).

The TCZ administration criteria were severe pneumonia caused by COVID-19 and presence of one of the following laboratory parameters IL-6 >40 uL/L, D-dimer >1500 mcg/mL or if patient exhibited persistently rising D-dimer parameter. Patients with liver enzymes five times over the upper limit of normality or concomitant severe bacterial infection were not eligible for TCZ treatment (12). The final decision to use TCZ was at the discretion of the treating clinician.

All patients admitted in the hospital with confirmed COVID-19 infection were treated with a standard pharmacological protocol including antiviral drugs, antibiotic prophylaxis. Tocilizumab was initialy administered at a dosage of 8 mg/kg max 800 mg by two

consecutive administrations 12 h apart (12).

Data Collection

Demographic data, comorbidities, mechanical ventilator treatment process, complications (such as pneumothorax pneumomediastinium, emphysema, pulmonary embolism), length of hospital stay, length of stay in intensive care unit (ICU), and survival data of all patients included in the study were analyzed. These data were analyzed and evaluated separately in patients who received and did not receive TCZ treatment.

Outcomes

The primary end point forthis analysis was all cause mortality. Death was assessed as occurring during hospitalization. Secondary outcomes included in lenght of hospital and ICU stay. Lenght of hospital stay was calculated from day of admission to the day discharge alive.

Statistical Analysis

This study was designed to investigate the effect of TCZ administration on the outcomes of these patients, using the propensity score matching (PSM) method to eliminate the influence of other confounding factors. To minimize indication bias patients to be included in each analysis were selected by matching their individual propensity for receiving therapy with TCZ, conditional on their demographic and clinical variables. The following variables were fitted to a logistic regression model to derive their propensity score: age, sex, asthma/chronic obstructive pulmonary disease (COPD), obesity, hypertension, diabetes, cancer, chronic renal failure and a ratio of arterial oxygen saturation measured by pulse oximetry to fraction of inspired oxygen (SpO_2/FiO_2). The variable was the worst SpO_2/FiO_2 within the first 72 h after admission. PSM were performed to account for counfounding by indication bias in the logistic regression model analysis. Other characteristics and outcomes of the patients compared using Students' t test and chi square test. Statistical analysis were performed using IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY) and statistical significance was set as $P < 0.05$.

Tocilizumab Treatment

TCZ treatment is applied in accordance with the guideline published by our Ministry of Health in patients who do not respond to systemic corticosteroid treatment in severe disease course or cytokine storm syndrome in COVID-19 infection (12). TCZ can be administered at a dose of 8 mg/kg and depending on the severity of the disease, it can be administered as 400 mg or 800 mg IV (maximum 800 mg) at a time. After the application, the clinical and laboratory parameters of the patient are followed. If necessary, a repeat dose of 200-400 mg can be administered within 24 hours after the first administration.

TCZ treatment should not be applied to pregnant women, patients with active tuberculosis and active hepatitis B, hepatitis C, patients with neutropenia (<500/mm3) in laboratory results, and patients with allergy and hypersensitivity reaction (12). Patients with a history of diverticulitis should be followed closely for the development of gastrointestinal perforation during TCZ treatment. During the TCZ treatment process, laboratory findings such as platelet count and liver function tests of the patients should be followed closely and TCZ treatment should not be applied to patients whose liver function tests are above five times the normal value (12).

A volume equal to the TCZ concentration to be applied to the patient is withdrawn from a sterile 100 ml SF (0.9% isotonic sodium chloride) solution. For example, 10 ml for 200 mg, 20 ml for 400 mg, 40 ml for 800 mg. The amount of TCZ to be applied to the patient is withdrawn from the vial and added to the 100 ml infusion bag. The final volume of the infusion fluid should be 100 ml. The solution is mixed slowly without foaming and infusion therapy is applied to the patient at a rate of 100 cc/h.

RESULTS

A total of 589 patients, 565 of whom were admitted to the hospital between 01.09.20 and 01.01.21, were included in the analysis. After exclusion of patients hospitalized for <24 h (n=12) for no need of oxygen therapy >36 h (n=12) or other exclusion reasons. Among the included individuals 517 (91.5%) patients were included in the control group, 48 (8.5%) were treated with TCZ. Characteristics of the patients included in the study are listed in **Table 1**.

In unmatched analysis the ICU stay was longer in patients treated with TCZ (9.3 vs. 7.2 days respectively $P<0.05$). Overall mortality in the patients was 71.5% and no differences were found in mortality between the groups (60.4% vs. 72.5%). Mean outcomes differences before matching are showed in **Table 2**.

TCZ and control group were well matched after propensity score (PS), comparison of PS distributions is shown in **Table 3**.

After matching the results showed no tendency towards the association between TCZ use and hospital lenght of stay. After PS analysis no difference in overall hospital mortality was noted between TCZ and control group. Mean outcomes differences after matching are listed in **Table 4**.

Table 1. Characteristics of the patients at cohort entry

Characteristics	Total (n = 565)	TCZ (n= 48)	Control (n =517)	P value*
Age (years ±Sd)	**71.2±12.2**	**71.8±12.1**	**64.8±11.6**	**<0.001**
Male sex	336 (59.5%)	28 (58.3%)	308 (59.6%)	0.989
Obesity	**141 (25.0%)**	**21 (43.8%)**	**120 (23.2%)**	**0.003**
Asthma/COPD	174(30.8%)	15 (31.2%)	159 (30.8%)	0.943
Cancer	19 (3.4%)	1 (2.1%)	18 (3.5%)	1.000
Hypertension	368 (65.1%)	22 (54.2%)	342 (66.2%)	0.131
Diabetes	255 (45.1%)	23 (47.9%)	232 (44.9%)	0.800
Coronary artery disease	174 (30.8%)	14 (29.2%)	160 (30.9%)	0.926
Chronic renal failure	15 (2.7%)	0 (0.0%)	15 (2.9%)	0.629
SpO_2/FiO_2 ratio ±Sd	77.0±39.2	71.9±37.6	77.4±39.0	0.350

*P value obtained comparing tcz group with control group. List of abbreviations: COPD=Chronic Obstructive Pulmonary Disease, TCZ=Tocilizumab

Table 2. Mean outcomes differences before matching

All cohort outcomes	Total (n=565)	TCZ (n=48)	Control (n=517)	P value*
Mechanical ventilation	413 (73.1%)	35 (72.9%)	378 (73.1%)	0.976
Pneumothorax, Pe, Pnmed, emphysema	48 (8.5%)	4 (8.3%)	44 (8.5%)	1.000
In hospital stay	13.3±7.7	15.2±6.7	13.1±7.7	0.066
ICU stay	**7.4±4.7**	**9.3±5.4**	**7.2±4.6**	**0.011**
In hospital mortality	404 (71.5%)	29 (60.4%)	375 (72.5%)	0.107

*P value obtained comparing tcz group with control group. Data are presented as n (%) unless vontinious variables (days) presented as mean ±Sd, List of abbreviations: Pnx=Pneumothorax, Pe=Pulmonary embolism, Pnmed=Pneumomediastinium, TCZ=Tocilizumab, ICU=Intensive care unit

Table 3. Patients characteristics after matching

Characteristics	Total (n = 96)	TCZ (n= 48)	Control (n =48)	P value*
Age (years ±Sd)	**58.3±14.7**	**64.8±11.6**	**52.0±14.8**	**<0.001**
Male sex	55 (57.3%)	28 (58.3%)	27 (56.2%)	0.837
Obesity	**57 (59.4%)**	**21 (43.8%)**	**36 (75.0%)**	**0.002**
Asthma/COPD	30 (31.2%)	15 (31.2%)	15 (31.2%)	1.000
Cancer	2 (2.1%)	1 (2.1%)	1 (2.1%)	1.000
Hypertension	48 (50.0%)	26 (54.2%)	22 (45.8%)	0.414
Diabetes	48 (50.0%)	23 (47.9%)	25 (52.1%)	0.683
Coronary artery disease	27 (28.1%)	14 (29.2%)	13 (27.1%)	0.820
SpO_2/FiO_2 ratio ±Sd	71.5±32.3	71.9±37.5	71.1±26.5	0.906

*P value obtained comparing tcz group with control group. List of abbreviations: COPD=Chronic Obstructive Pulmonary Disease, TCZ=Tocilizumab

Table 4. Mean outcomes differences after matching

All cohort outcomes	Total n=(96)	TCZ (n=48)	Control (n=48)	P value*
Mechanical ventilation	67 (69.8%)	35 (72.9%)	32 (66.7%)	0.505
Pnx, Pe, Pnmed, emphysema	8 (8.3%)	4 (8.3%)	4 (8.3%)	1.000
In hospital stay	14.9±7.8	15.2±6.7	14.5±8.9	0.661
ICU stay	8.6±5.3	9.3±5.4	7.9±5.1	0.198
In hospital mortality	59 (61.5%)	29 (60.4%)	30 (62.5%)	0.834

*P value obtained comparing tcz group with control group. Data are presented as n (%) unless vontinious variables (days) presented as mean ±Sd, List of abbreviations: Pnx=Pneumothorax, Pe=Pulmonary embolism, Pnmed=Pneumomediastinium, ICU=Intensive care unit, TCZ=Tocilizumab

DISCUSSION

In this study, we examined the effects of TCZ treatment on length of hospital stay, length of ICU stay, and mortality in patients with COVID-19 infection. We found that the mean age of the patients who underwent TCZ treatment after PSM was significantly higher than the control group. Cytokine storm is a condition that occurs with the uncontrolled proliferation of proinflammatory markers in the human body. These proinflammatory markers such as IL-6 and IL-8 increase in circulation when cell death is about to occur. In elderly patients, the inflammatory signaling process is faster in these patients because of aging-related changes in cells and cellular changes caused by comorbidities (13). Therefore, these patients are more prone to cytokine storms because of the weaker adaptive immune response and the faster rise of proinflammatory markers in their circulation (13). We think that this is the reason for the higher average age of the patients who received TCZ treatment in our study. Severe anorexia and adipsia due to cytokine increase are common in elderly COVID-19 patients (14). A

meta-analysis concluded that obesity increases the risk of severe COVID-19 infection and increases in-hospital mortality rates in COVID-19 infection (15). Chronic diseases such as diabetes and coronary artery disease increase the risk of severe COVID-19 infection (13). Since obesity increases the risk of developing chronic diseases (such as diabetes, coronary artery disease), obesity is also thought to have a high risk of developing severe COVID-19 infection (16). The results of our study showed that the mean body mass index (BMI) of patients who received TCZ treatment because of severe disease was lower than those who did not receive TCZ treatment.

In the study of Shcherbak et al. (17), male gender and being over 40 years of age were found to be among the predisposing factors for cytokine storm in COVID-19 patients. In our study, no significant difference was found between the genders of the patients who received and did not receive TCZ treatment. Although male gender is among the predisposing factors for cytokine storm, it did not reveal a significant difference between female gender in the development of severe disease and the application of TCZ treatment due to cytokine storm.

Cytokine storm syndrome was more common during COVID-19 infection in patients with comorbidities such as diabetes, hypertension, chronic renal failure, asthma, chronic arterial disease, and cancer (13,18). In the study of Guaraldi et al. (18), patients receiving TCZ treatment were more likely to have comorbid diseases such as diabetes, hypertension, and chronic kidney failure, whereas in our study, no significant difference was found between patients who received TCZ treatment and those who did not.

In the randomized clinical study of Salvarani et al. (19), patients with COVID-19 pneumonia with a PaO_2/FiO_2 ratio of 200-300 mmHg were selected. In other words, research has been done on the effectiveness of TCZ treatment at an earlier stage, but it has not been seen that early TCZ treatment has a significant effect in reducing the need for intubation or mortality. Campochiaro et al. (20), no significant difference was found between patients who received and did not receive TCZ treatment in terms of clinical improvement and mortality, but it was observed that TCZ treatment initiated in patients with a PaO_2/FiO_2 ratio above 100 provided higher clinical improvement. In our study, the mean values of the patients whose SpO_2/FiO_2 ratios were recorded were found to be approximately 71 mmHg after PSM in both groups who received and did not receive TCZ treatment, and there was no statistically significant difference between the two groups. There are studies that suggest that the use of SpO_2/FiO_2 ratio may also be reliable in predicting early invasive mechanical ventilation (21). Different studies have tried to decide on threshold values (21,22). When we examined, values of 100 mmHg and below are indicative of the development of severe disease and these patients are likely to need early mechanical ventilation. In our study, no significant difference was found between the patients who received and did not receive TCZ treatment in terms of the need for invasive mechanical ventilation. In other words, in our study, there was no additional benefit of TCZ treatment in reducing the need for invasive mechanical ventilation in patients with severe acute respiratory distress syndrome (ARDS). Klopfenstein et al. (23) showed that patients receiving TCZ treatment needed less invasive mechanical ventilation. In the study of Salama et al. (24) among patients with moderate and severe COVID-19 pneumonia, patients who received TCZ treatment combined with antiviral and glucocorticoids needed less mechanical ventilation than those who received placebo and combined antiviral, glucocorticoid. According to the results of the same study, there was no difference in mortality from any cause between patients who received and did not receive TCZ treatment. In a study conducted in patients who developed ARDS due to COVID-19 infection, complications such as pneumothorax, pneumomediastinium, emphysema, and hemothorax due to invasive mechanical ventilation were examined (25). No significant difference in mortality was reported between the group with and without mechanical ventilation-induced barotrauma. (25). It has been observed that these complications may occur due to the barotraumatic effect of mechanical ventilation, as well as non-barotraumatic due to inflammation, consolidation and necrosis in the lung tissue due to COVID-19 infection (26-28). In our study, no significant difference was found between the patients who received and did not receive TCZ treatment in terms of complications such as pneumothorax, pneumomediastinum, pulmonary embolism, and emphysema.

In our study, although the patients who received TCZ treatment had longer stays in the ICU and hospital, there was no statistically significant difference compared to the patients who did not receive TCZ treatment. There was no significant difference in in-hospital mortality rates between patients who received and did not receive TCZ therapy. Klopfenstein et al. (23), it was observed that TCZ treatment had no effect on hospitalization and length of stay, but significantly reduced mortality rates. In the study of Rosotti et al. (29) it was observed that TCZ treatment prolongs the length of hospital stay but reduces the mortality rate.

In a retrospective cohort study by Colaneri et al. (30) in Italy, no significant difference was found between the length of stay in the ICU and the seven-day mortality rates in patients who received and did not receive TCZ therapy. In a retrospective observational study, it was found that TCZ treatment shortened the length of stay and was associated with a decreased mortality rate (31). In a multicenter observational study, it was found that TCZ treatment reduced the mortality rate in COVID-19 patients hospitalized in the ICU (32). Rossi et al. (33) in a study conducted in Italy, mortality rates were found to be significantly lower in patients who received TCZ treatment.

In the placebo-controlled randomized study of Rosas et al. (34), no significant difference was observed in the 28-day mortality in COVID-19 patients who were started on early TCZ treatment compared to the placebo group. Hermine et al. (35) reported that as a result of their randomized clinical trial, TCZ treatment did not make a significant difference in the need for mechanical ventilation and 28-day mortality rate in COVID-19 patients. In the randomized, double-blind, placebo-controlled study of Stone et al. (36) it was also seen that TCZ treatment did not have an effect on 28-day mortality. In the study of Veiga et al. (37) they reported that they could not find a beneficial effect of TCZ treatment on clinical outcomes in patients with moderate-to-severe COVID-19 pneumonia. In addition, as a result of their analysis, they found that starting TCZ treatment early or late did not change the effect of treatment on clinical outcomes. A meta-analysis investigating the efficacy of TCZ therapy in COVID-19 patients found that TCZ therapy did not add any additional benefit to clinical outcomes (38).

As a result of the researches, we saw that there was no consensus on the results of TCZ treatment, and we conducted this cross-sectional retrospective study. Between the dates examined by the study, access to TCZ was not easy, and patients could be provided and treated within at least two days after they were admitted to the ICU. Patients hospitalized in the ICU had the development of severe ARDS. Although we cannot clearly determine the reason why TCZ treatment does not reduce the need for invasive mechanical ventilation and the mortality rate, we think that this may be related to the time we start treatment in patients with severe disease. Considering that the severity and mortality of COVID-19 is related to IL-6, it was expected that TCZ treatment, which is an IL-6 antagonist, would increase clinical recovery, shorten the length of stay and reduce mortality rates. As a result of a retrospective analysis, it was observed that there was a slight decrease in the mortality rate when TCZ was started in patients with low IL-6 levels, but a higher decrease in mortality rate was observed when it was started in patients with high IL-6 levels (39). If this treatment was applied to patients with low IL-6 levels, this may explain the results of our study. In our study, IL-6 levels were not measured before starting TCZ therapy. We cannot reveal data on this. In addition, the patients in our study were patients with severe COVID-19 infection, so we cannot make inferences about the clinical results of TCZ treatment before ICU admission or in the early stage of the disease.

Our study has limitations as it is a retrospective and single-center study. Mortality rates were evaluated during the hospitalization of the patients, and a long-term evaluation could not be made after discharge. The PSM model allowed us to reduce the resulting bias as it provided randomization. This model, which is used to match patients, cannot control the effect of variables that are not included in the matching (40).

CONCLUSION

A clear consensus has not yet been established on the effect of TCZ treatment on IL-6 receptor blockade and reducing inflammation. Although the COVID-19 pandemic has reduced its severity, its effects continue today and the disease has not been completely eradicated. We conducted our study in the hope of guiding clinicians in the treatment of the disease and scientists who will conduct a placebo-controlled randomized study in case the COVID-19 epidemic worsens or similar viral pandemics occur. The population that will benefit most from TCZ treatment, the timing, dose, regimen, and complications of treatment are still unclear. There is no consensus on treatments (anti-inflammatory, glucocorticoid, antiviral, etc.) combined with TCZ. Therefore, randomized controlled studies are needed to determine which patients will have the beneficial effect of TCZ treatment on the possible clinical outcome. At the same time, there is a need for randomized controlled clinical studies for the treatment of TCZ by creating a patient cytokine profile such as IL-6 level. This retrospective cross-sectional study showed that TCZ therapy had no beneficial or significant effect on any of the outcomes of invasive mechanical ventilation need, length of stay in hospital and ICU, and mortality in patients with severe disease development and hospitalized in the ICU. The results of larger, randomized, placebo-controlled studies are needed to understand the efficacy of tocilizumab in the treatment of COVID-19.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out with the permission of Uşak University Medical Faculty Clinical Researches Ethics Committee (Date: 15.06.2022, Decision No: 108-108-06).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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